October 12, 1999

MEMORANDUM

SUBJECT: **Thiabendazole**; P.C.Code 060101. The HED toxicology chapter for the Reregistration Eligibility Decision document (RED).
DP Barcode: D251076, Submission: S551722.

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Attached is the Toxicology chapter for thiabendazole, for purposes of issuing a Reregistration Eligibility Decision (RED) Document.

incl: Attachment
cc: Caswell File

HAZARD CHARACTERIZATION

Thiabendazole is a systemic fungicide used to control mold, rot, blight, and stain on fruits and vegetables. It is also active against storage diseases and Dutch Elm disease. In livestock, thiabendazole is also applied to treat roundworms. The toxicological data base for thiabendazole is complete and will support the reregistration eligibility decision (see Table 1).

Thiabendazole has low acute toxicity via the oral and dermal routes (Category III). It is not an eye or dermal irritant nor a dermal sensitizer.

The available database indicates that thiabendazole is not neurotoxic.

The thyroid and liver are the primary target organs of thiabendazole. In rat subchronic studies, oral administration of thiabendazole caused increased liver and thyroid weights and increased incidences of hepatic centrilobular hypertrophy and thyroid follicular cell hyperplasia and hypertrophy in both sexes.

In a chronic rat study, thiabendazole induced thyroid tumors in males. The Health Effects Division (HED) Cancer Assessment Review Committee (CARC) classified thiabendazole as "**likely to be carcinogenic to humans**." These tumors were attributed to interference with thyroid-pituitary homeostasis. No tumors were induced in mice.

There is no evidence of increased susceptibility of rat, rabbit, or mouse fetuses to *in utero* exposure in developmental studies. The effects observed in these species occurred at maternally toxic doses. There is no other evidence in the database that would suggest a requirement for a developmental neurotoxicity study with thiabendazole.

The acceptable genetic toxicology studies on thiabendazole indicate that it is non-genotoxic/mutagenic *in vivo* and *in vitro* assays. Review of literature studies indicated that thiabendazole has weak aneugenic activity in both somatic and germinal cells.

Thiabendazole is readily absorbed by male and female rats following oral dosing. Renal excretion is the primary pathway for the elimination of thiabendazole in rats. Excretion of thiabendazole in the urine and feces is rapid in most species and is almost complete after 48 hours in rats and 96 hours in sheep. The primary metabolites were the glucuronide conjugate of 5-hydroxythiabendzole and the sulfate conjugate of 5-hydroxythiabendazole. Minor amounts ($\leq$1% of the dose) of free 5-hydroxythiabendazole were present in urine from rats from all dose groups.

TABLE 1: REGULATORY PROFILE OF THIABENDAZOLE TECHNICAL

GUIDELINE	STUDY TYPE	REQUIRED	SATISFIED	MRID (or Accession No.)
81-1	Acute Oral	Yes	Yes	41258201
81-2	Acute Dermal	Yes	Yes	41258202
81-3	Acute Inhalation*	Yes	Waived	
81-4	Primary Eye Irritation	Yes	Yes	40789806
81-5	Primary Dermal Irritation	Yes	Yes	40789807
81-6	Primary Dermal Sensitization	Yes	No	40271701
81-8	Acute Neurotoxicology	Yes	Waived	
82-1 (a)	90-Day Feeding (rodent)	Yes	Yes	42942802
82-1 (a)	90-Day Gavage (rodent)	Yes	Yes	42942801
82-1 (b)	90-Day Feeding (dog)	Yes	Yes	42993601
82-2	21 -Day Dermal (rabbit)	Yes	Yes	41259501
83-2(b)	Oncogenicity (mouse)	Yes	Yes	00031447
83-5a	Chronic Feeding/Oncogenicity (rat),	Yes	Yes	43593201
83-1 (b)	Chronic Feeding (dog)	Yes	Yes	42809701
83-3 (a)	Developmental (rat)	Yes	Yes	42942803
83-3(b)	Developmental (rabbit)	Yes	Yes	42942804,42993602, 42942807
83-3(c)	Developmental (mice)	Yes	Yes	43753701, 43753702
83-4	Reproduction, 2 Gen (rat)	Yes	Yes	43190301
84-2(a)	Gene Mutation - Ames	Yes	Yes	42361801
84-2(b)	Chromosomal Aberration	Yes	Yes	43328304
84-2	Other: Mutagenic - DNA damage/repair	Yes	No	41170103
N/A	Thyroxine clearance (rat)	Yes	Yes	43593202
85-1	General Metabolism	Yes	Yes	42114701

*Waived for thiabendazole hypophosphite salt-20% a.i. (End use product)

a. Acute Toxicity

Acute toxicity values for thiabendazole in experimental animals as well as Toxicity Categories are summarized in Table 2. Thiabendazole has low acute toxicity (Category III) and is neither irritating to the eyes or skin nor a dermal sensitizer.

Table 2. Acute Toxicity of Thiabendazole

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	41258201	LD_{50} = 4735 mg/kg	III
81-2	Acute Dermal	41258202	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	Waived	HED Doc. No. 010140	
81-4	Primary Eye Irritation	40789806	Non-irritating	IV
81-5	Primary Skin Irritation	40789807	Non-irritating	IV
81-6	Dermal Sensitization	40271701	Non-sensitizer	IV
81-8	Acute Neurotoxicity	Waived	HED Doc. No. 006934	

b. Neurotoxicity

The available database indicates that thiabendazole is not neurotoxic. A requirement for an acute neurotoxicity study was waived by the Agency.

c. Subchronic Toxicity

In a 21-day dermal toxicity study, thiabendazole (98.9%) was administered dermally to 5 Nra:(NZW) SPF rabbits/sex/dose daily, at dose levels of 0, 50, 200, 1000 mg/kg/day. The test material was applied to a shaved area 6 hours per day, 7 days/week for either 21 or 22 days. No treatment-related mortality was observed. No systemic or dermal toxicities were noted at doses up to 1000 mg/kg/day (Limit dose) . **The LOAEL for systemic toxicity is > 1000 mg/kg/day**. **The systemic NOAEL is 1000 mg/kg/day. The dermal toxicity LOAEL 1000 mg/kg/day. The dermal NOAEL is 1000 mg/kg/day** (MRID 41259501)**.**

In a subchronic toxicity study, thiabendazole (99.4% a.i.) was administered to Crl:CD(SD) albino rats (10/sex/dose) in the diet at nominal dose levels of 10, 40, 160, or 320 mg/kg/day (achieved doses: 0, 9.4, 37, 149, and 302 mg/kg/day for males; 0, 9.4, 38, 152, and 302 mg/kg/day for females) for 13 weeks. **The LOAEL for this study is 40 mg/kg/day (37 mg/kg/day), based on reduced body weight gains and**

histopathological changes in the bone marrow, liver, and thyroid. The NOAEL is 10 mg/kg/day (9.4 mg/kg/day) (MRID 42942802)**.**

In another subchronic toxicity study thiabendazole was administered to Crl:CD(SD) albino rats (20/sex/dose) by gavage at dose levels of 0, 25, 100, or 400 mg/kg/day for 14 weeks. **The LOAEL for this study is 100 mg/kg/day, based histopathological changes of the liver, thyroid, kidneys, and spleen. The NOAEL is 25 mg/kg/day** (MRID 42942801).

In a subchronic toxicity study in dogs, thiabendazole (99.4% a.i.) was administered orally in capsules to four beagle dogs/sex/dose at dose levels of 0, 35, 75, or 150 mg/kg/day for 14 weeks. Thiabendazole produced concentration-dependent increases in the incidence of emesis in the 75 and 150 mg/kg/day treatment groups. Post-mortem evaluations did not reveal any treatment-related changes organ weights or gross pathological findings; however, microscopic lesions were observed in the gallbladders. An increase of gallbladder epithelial cytoplasmic vacuolation in the mid- and high-dose groups over the background incidence may have been treatment-related. **The LOAEL for this study is equivocal because the toxicological significance of emesis and gall bladder epithelial cytoplasmic vacuolation could not be determined. Therefore, the NOAEL is 150 mg/kg/day** (MRID 42993601)**.**

d. Chronic toxicity

In a chronic toxicity study, thiabendazole (99% a.i.) was administered orally in capsules to four beagle dogs/sex/dose at dose levels of 0, 10, 40 or 160 mg/kg/day for 52 weeks. Dogs lost weight during the first half of the study primarily due to emesis. One mid-dose male dog died of acute hepatitis after two weeks of treatment. At terminal sacrifice, treatment-related changes in organ weights and incidence of histopathological findings were observed.

Histopathological evaluations identified lesions in the liver, thyroid, gallbladder, kidney, urinary bladder and spleen. Livers exhibited slight to moderate bile duct vacuolation in mid- and high-dose animals. Thyroids had very slight follicular enlargement high-dose females, while very slight to slight follicular cell hypertrophy was observed in high-dose males and females. Dogs in the 10, 40 and 160 mg/kg/day treatment groups had gallbladders which exhibited cytoplasmic lipid vacuolation and discolored foci of the mucosa; dose-related increases in severity were observed. The kidneys of mid- and high-dose females showed very slight to slight distal tubule vacuolation, compared to females each in the control and low-dose groups. Urinary bladders of all high-dose dogs had very slight to slight epithelial cytoplasmic inclusions; this finding was also observed in males and females in the mid-dose group. The toxicological significance of the above findings could not be determined. Spleens exhibited very slight to slight increases in erythropoiesis in mid- and high-dose animals; hemosiderin deposits were observed in mid- and high-dose

animals. **The LOAEL for this study is 40 mg/kg/day, based on increased liver weight, splenic erythropoiesis and hemosiderosis in both sexes. The NOAEL is 10 mg/kg/day** (MRID 42809701).

e. Carcinogenicity

In a chronic toxicity and carcinogenicity study, thiabendazole was administered to 50 Sprague-Dawley Crl:CD BR rats/sex/dose in the diet at dose levels of 0, 10, 30, or 90 mg/kg/day (achieved average doses of 0, 10.1, 30.2, or 91.8 mg/kg/day) for 104 weeks. The systemic LOAEL is 30 mg/kg/day based on reduced body weights and body weight gains and liver hypertrophy (males). The systemic NOAEL is 10 mg/kg/day. Body weights and body weight gains were generally lower (7-30%) throughout the study for the mid- and high-dose males and high-dose females. Reduced body weight gains (15, 28, and 19%, $p \leq 0.05$) for the mid- and high-dose males and high-dose females, respectively, compared to the controls were observed at week 103. A reduced body weight gain (10%, not statistically significant) was also noted at this time for the mid-dose females.

Significant increases (36-79%) in total serum cholesterol observed in the high-dose group were judged to be treatment-related. In the high-dose males, increased (29%) relative (to body) liver weights and an increased incidence of centrilobular hepatocellular hypertrophy were also detected. Centrilobular hepatocellular hypertrophy was also observed in 7/50 mid-dose males. In the high-dose females, an increased (45%) relative thyroid weights and increased incidences of thyroid focal cystic follicular cell hyperplasia (6/50 treated vs 2/50 controls) and diffuse follicular cell hypertrophy (2/50 treated vs 0/50 controls) were observed. Thyroid diffuse follicular cell hypertrophy was also observed (4/50 treated vs 0/50 controls) in the high-dose males.

An increase in benign thyroid follicular cell adenoma was observed in the mid-dose (5/50) and high-dose (6/50) males (vs 0/50 controls) and the high-dose females (5/50 treated vs 2/50 controls). The increase was statistically significant ($p \leq 0.05$) in the high-dose males. Also, in the male rats, there was a statistically significant trend ($p \leq 0.05$) in the incidence of thyroid follicular cell adenomas with increasing dose. No statistically significant trend in the incidence of any other neoplasm in either sex was observed (MRID 43593201). Thiabendazole may affect the rat thyroid indirectly by altering thyroxine clearance via increased hepatic metabolism. This mechanism is specific to the rat. The Sponsor has submitted for Agency review a 14 week thyroxin clearance study (MRID 43593202) in support of this hypothesis.

The study demonstrated that thiabendazole induces thyroid adenomas in male rats at dosages of 30 mg/kg/day (MRID 43593201).

In a carcinogenicity study, thiabendazole was administered to 50 mice (Charles River CD-1)/sex /dose in diet at dose levels of 0, 5.6-8.3, 31-42, 63-121, 184-372 mg/kg/day for males and 0, 5.7-9.9, 94-131, 209-368, and 534-1005 mg/kg/day for females for 105 weeks. There was an increase in mortality in all dose groups. Body weight gains were significantly lower in high dose females (28%) and males (18%). There was an increase in the absolute liver weight of high-dose females, and an increase in the relative liver weight in mid-dose females and high-dose males and females. There was an increase in the relative liver: brain weight ratio in high-dose males and females.

It was noted that there were sufficient numbers of animals alive at both time intervals to assess the carcinogenic response. However, no treatment-related increase in tumor incidence above background level was observed. Although the dosing was variable, a compound-related effect (i.e. increased mortality) was noted in both sexes at the mid- and high-dose groups at 18 months and at the high-dose group at 15 months, assuming that the animals received the lowest dose of the range for each dose group. Therefore, the dosing was considered to be adequate, and the study was acceptable (MRID 00031447).

f. Developmental Toxicity

Developmental effects by thiabendazole in rabbits, rats, and mice occurred at the same dose levels that caused inhibition of ChE activity in maternal animals.

In the rat developmental study, there were significant decreases in maternal mean body weights and feed consumption noted at 40 and 80 mg/kg/day. The female fetal body weights were decreased at 40 mg/kg/day and in males at 80 mg/kg/day. Therefore, the rat maternal and developmental LOAEL/NOAEL are 40/10 mg/kg/day, respectively (MRID 42942803).

In the mouse prenatal developmental toxicity study, there were reductions in maternal body weight at mid (100 mg/kg/day) and high dose (200 mg/kg/day)dose treatment groups. There were accompanying reductions in feed consumption in the HDT group. There was decreased fetal body weight at 100 mg/kg/day for both sexes. The mouse maternal and developmental LOAEL/NOAEL are 100/25 mg/kg/day, respectively (MRID 43753701).

In the rabbit developmental study, decreased maternal body weight gains and decreased food consumption were seen in the HDT (600 mg/kg/day). There was decreased fetal body weight and increased resorptions at 600 mg/kg/day. The rabbit maternal and developmental LOAEL/NOAEL are 600/150 mg/kg/day, respectively (MRID 42942804).

The benzimidazole compounds such as parbendazole, cambendazole and mebendazole posssess tertogenic and embryotoxic properties. The studies in the published literature indicate that thiabendazole can cause developmental effects after single in utero exposure

of pregnant animals at high doses. However, these studies do not suggest that fetuses are selectively susceptible following in utero exposure to thiabendazole. These studies are summarized below.

1). In a teratogenicity study in rats (Khera et al., 1979), thiabendazole administered to dams from GD 6-15 at doses ranging from 125 to 500 mg/kg/day produced increased incidence of anomalous fetuses at the highest dose (500 mg/kg/day) level. No details on maternal effects were reported.

2). The developmental toxicity of thiabendazole (TBZ) was assessed in Sprague-Dawley rats and New Zealand (NZB) rabbits (Lankas and Wise, 1993). Rats received TBZ at 10, 40, or 80 mg/kg/day and rabbits received TBZ orally at doses ranging from 24 to 600 mg/kg/day (in two studies) as an aqueous suspensions on GD 6-17.

TBZ produced decreased maternal body weight gain (12 to 26%) and decreases in fetal body weights (5-7%) at doses of 30 and 80 mg/kg/day. NOAEL was 10 mg/kg/day and no teratogenic effects were noted.

In rabbits, decreased maternal weight gain and decreased fetal weights were noted at 600 mg/kg/day, but there was no evidence of developmental anomalies. The NOAEL was 120 mg/kg/day.

3). Thiabendazole was administered orally in olive oil (Ogata et al., 1984) to pregnant Jcl:ICR mice at doses of 700, 1300 or 2400 mg/kg/day TBZ on GD 7-15. No maternal effects were reported in this study. A dose-dependent external and skeletal anomalies, especially cleft palate (although in a non-dose related manner) and fusion of vertebrae, were observed. In mice given single dose of 2400 mg/kg/ TBZ on any one of the GD 6-13, an increased number of malformations were observed. Various malformations occurred, especially in the mice treated on GD 9. Groups of mice given one of the 17 doses (30-2400 mg/kg) on GD 9, the number of litters with fetuses having shortened limbs and fetuses with skeletal fusion increased in a dose-related manner. Based on these findings FAO/WHO recommended that the acceptable daily intake (ADI) of TBZ should be 0.05 mg/kg.

4). In a 2-Generation reproduction study (Wise et al., 1994), Sprague-Dawley rats received TBZ at dietary doses of 10, 30 or 90 mg/kg/day during premating, gestation and lactation. The parental toxicity was seen at 30 mg/kg/day based on decreased body weight gain (37-46%) and food consumption (3-16%) . The NOAEL was 10 mg/kg/day. Decrease in pup body weight (5-10%) was noted between postnatal days 4 and 21. The NOAEL was 10 mg/kg/day. Thus, no selective sensitivity to TBZ was noted in pups.

g. Reproductive Toxicity

In the two generation reproduction study conducted with Sprague Dawley rats, thiabendazole was administered at doses of 0, 10, 30, or 90 mg/kg/day (achieved doses of 9.4-9.8, 28.1-29.3, or 84.1-85.9 mg/kg/day). The parental systemic LOAEL is based on decreased body weight gain and food consumption seen at 30 mg/kg/day. The NOAEL is 10 mg/kg/day. The offspring LOAEL is based on decreased body weight gain in offspring during lactation seen at 30 mg/kg/day. The NOAEL is 10 mg/kg/day. The reproductive LOAEL is > 90 mg/kg/day. The effects in the offspring were observed at higher dosages (90 mg/kg/day) than dosages (30 mg/kg/day) causing parental toxicity. Therefore, there was no increased susceptibility (MRID 43190301).

h. Mutagenicity

Of the several mutagenicity studies submitted, three were acceptable/guideline. These studies plus other acceptable/nonguideline studies indicate that thiabendazole is not a mutagen and are summarized in Table 3 below.

Table 3. Mutagenicity Profile for Thiabendazole

Guideline #	TYPE OF STUDY SUBMITTED	MRID No(s)	Comments
84-2	Chromosome aberration assay	00098002	*In vivo* cytogenetic assay: The test was negative in Wistar rats admnistered single doses of 10-1000 mg/kg by oral gavage or 30-300mg/kg once daily for 5 consecutive days. Lethality was seen in the high-dose group but there was no evidence of bone marrow cytotoxicity.
84-2	Chromosome aberration assay	43328304	In an *in vivo* bone marrow chromosome aberration assay, male CRL:CD-1 mice were given a single oral dose of Thiabendazole (99.8% purity) in methylcellulose at levels of 200, 667, and 2,000 mg/kg bodyweight. Bone marrow was sampled 6, 24, and 48 hours after treatment. All mice survived to their scheduled termination and clinical signs of toxicity were noted at 667 and 2,000 mg/kg. There were no significant increases in the incidence of chromosome aberrations at any sampling time. The positive control induced significant increases in cells with chromosome aberrations.
84-2	Chromosome abberation assay	00125297	*In vitro* mammalian cell cytogenetic assay in WI-38 human fibroblasts. The test is negative up to precipitating levels (1000 g/mL) without S9 activation.
84-2	Mutagenic -Ames	42361801	Five doses of thiabendazole ranging from 100ug/plate to 6000 ug/plate +/-S9, did not induce mutations in Salmonella typhimurium strains TA 1535, TA97A, TA98, or TA100 and Escherichia soli strains WP2, WP2 UvrA, or WP2 uvrA pKM101. Compound precipitation and cytotoxicity for the majority of strains was observed at levels 1000 ug/plate +/-S9. Similar results were obtained in a repeat assay conducted in three strains (S.typhimurium TA 97Aand E.coli WP2 uvrA and WP2 uvrA pKM101) with a lower dose range (3-300 ug/plate +/-S9). Based on these findings, it was concluded that thiabendazole was tested over an appropriate range of concentrations and was not genotoxic.

84-2	Mutagenicity / DNA damage/repair	41170103 (Nonguideline)	In a DNA damage/repair assay, the test material was first assayed in a cytotoxicity test (MRID No. 41170103) employing trypan blue exclusion as a measure of cell viability in cultures exposed for 3 hours at concentrations up to precipitating levels (ca. 1.3 mM) in culture medium (Leibowitz, L-15). Concentrations selected for testing in the main assay were 0.3, 0.7, 1.0, and 1.3 mM, applied for 3 hours to duplicate monolayer cultures of hepatocytes, following which cells were gently scraped from culture dishes and suspended in fresh medium. Cell viability was determined from a small aliquot, and the remainder lysed and fractionated under tetrapropyl ammonium hydroxide, then eluted for fluorometric determinations of DNA according to conventional (published) procedures. Aflatoxin B1 (AFL, 1 uM) in DMSO served as the positive control. Data from these fractions were transformed into elution slopes, which were then compared to known standards, according to the following criteria for defining positive results. At none of the concentrations tested (0.3 to 1.3 mM) did the test material produce a significant (at least threefold) increase in elution slope relative to concurrent negative control. By contrast, the positive control, AFL produced a twentyfold increase, indicating that the cells were responding to a known strand-breaking mutagen. **Based on these results the author concluded that thiabendazole did not induce DNA strand breakage in primary rat hepatocytes exposed to concentrations up to the level of its insolubility in culture medium.**

In contrast to the negative findings from the acceptable studies, thiabendazole has been shown by several investigators in the published literature to induce micronuclei in mouse bone marrow with 75% of the scored micronuclei staining positive for kinetochore (KC+). The finding of increased KC+ micronuclei suggests an aneuploidy effect (adverse effects on chromosome numbers) since micronuclei staining positive for kinetochore are presumed to contain intact chromosomes while those staining negative for kinetochore contain chromosome fragments resulting from structural chromosome damage (i.e., a clastogenic effect). There is also evidence from the literature that thiabendazole induces aneuploidy not only in somatic cells *in vivo* but also in germinal cells (secondary spermatocytes and oocytes) of whole animals at high toxic doses. Thiabendazole has also been shown to inhibit the *in vitro* polymerization of porcine brain tubulins; this finding is in agreement with the proposed mechanism by which benzimidazole-related chemicals induce aneuploidy through interference with microtubule assembly. Similarly, the positive results from the *in vivo* micronucleus assays are consistent with the data from other benzimidazole analogs (e.g., the common metabolite of benomyl and thiophanate-methyl, methyl-2-benzimidazole carbamate, MBC and benomyl) indicating that these compounds are confirmed inducers of aneuploidy.

i. Metabolism

In a rat metabolism study (MRID 42114701), [phenyl-U-^{14}C]thiabendazole (99.1% a.i.) was administered to five Crl:CD BR strain rats/sex/dose by gavage as a single dose at 25 or 400 mg/kg or as a single dose at 25 mg/kg following a 14-day pretreatment with unlabeled thiabendazole at 25 mg/kg.

[^{14}C]Thiabendazole was readily absorbed by male and female rats following oral dosing. The rate of urinary excretion for both sexes in the high dose groups was lower during the initial 24 hours compared to the low dose groups. For all test groups, 51-73% of the dose was excreted in the urine during the first 48 hours. Dose rate and pretreatment with thiabendazole had no apparent effect on absorption. Within 168 hours of dosing at 25 mg/kg (with or without pretreatment) or 400 mg/kg, 94.3-98.9% of the administered dose was recovered from both sexes, of which 67.3-74.6% was in the urine, 21.3-26.7% was in the feces, and 0.3-2.5% was in the cage washes.

The data indicate that renal excretion is the primary pathway for the elimination of thiabendazole from rats. At the low dose level, it was shown that thiabendazole oxidizes to form 5-hydroxythiabendazole, followed by conjugation to form glucuronide and sulfate conjugates of 5-hydroxythiabendazole.

a. Dermal absorption

No dermal absorption studies are available.

Hazard Endpoint Identification

On June 1 and 17, 1999, the Health Effect Division's (HIARC) Hazard Identification Assessment Review committee (HIARC) reviewed the toxicology database for thiabendazole and selected doses and toxicology endpoints for risk uncertainty factors and margins of exposures for dietary and non-dietary risk assessments , based solely on animal toxicity studies. The latest HIARC report (HED Doc. No. 013601) supersedes earlier RfD, TES, and HIARC reports for thiabendazole. Table 4 provides a summary of toxicology endpoint selection and Margins of Exposure based on this report. The HIARC recommended that a factor of 10 be removed since there is no evidence of increased fetal susceptibility in the mice, rat, and rabbit developmental studies.

Table 4. The doses and toxicological endpoints selected and Margins of Exposure for various exposure scenarios for thiabendazole.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE[a]

Acute Dietary	NOAEL= 10 (♀13+) UF = 100	Decreased fetal body weight.	Oral Developmental / Rat	Not relevant
	NOAEL= 10 (Gen. Pop'n) UF= 100	Decreased maternal body weight seen during gestation.	Oral Developmental / Rat	Not relevant
	Acute RfD (♀ 13+) = 0.1 mg/kg/day Acute RfD (Gen. Pop'n) = 0.1 mg/kg/day			
Chronic Dietary	NOAEL = 10 UF = 100	Decreased body weight gains and liver hypertrophy.	Combined Chronic Toxicity-Carcinogenicity / Rat	Not relevant
	Chronic RfD = 0.01 mg/kg/day			
Cancer	Use non-linear extrapolation	Increased incidence of thyroid follicular cell adenomas and combined adenomas/carcinomas. Point of departure = 10 mg/kg/day	Combined Chronic Toxicity-Carcinogenicity / Rat	b
Dermal Absorption	Correction for oral to dermal exposure necessary (60% dermal absorption factor).			
Short-Term (Dermal)	Oral NOAEL= 10	Decreased fetal body weights.	Oral Developmental / Rat	100
Intermediate-Term (Dermal)	Oral NOAEL= 5	Reduced body weight gains and histopathological changes in the bone marrow, liver, and thyroid.	14-week Oral Toxicity / Rat	100
Long-Term (Dermal)	Oral NOAEL = 10	Decreased body weight gains and liver hypertrophy.	Combined Chronic Toxicity-Carcinogenicity / Rat	100
Conversion of inhalation exposure to oral dose (100% lung absorption factor) and dermal exposure to oral dose (60% dermal absorption factor) is necessary.				
Inhalation (Any Time Period)	Oral NOAEL = 10	Increased liver weight, splenic erythropoiesis, and hemosiderosis.	Chronic (Feeding) Toxicity / Dog	100

a. MOEs are for occupational and residential exposure risk assessments.
b.Acceptable MOE for cancer risk has not been determined.

1a. Acute Reference Dose (RfD) established for **Females 13-50 years of age**

Study Selected: Developmental Study–Rat (§83-3a), MRID No.42942803
Dose and Endpoint for Establishing RfD: The developmental NOAEL is 10 mg/kg/day based on decreased fetal body weight at 40 mg/kg/day (LOAEL).
Uncertainty Factor (UF): 100

Acute RfD: $\frac{10 \text{ mg/kg}}{} = \mathbf{0.1 \text{ mg/kg}}$

100 (UF)

Comments about Study/Endpoint/Uncertainty Factor: The decreased fetal body weight are presumed to occur after a single exposure (dose) and was also seen in studies with other species (mice and rabbits). Therefore, this endpoint is considered to be appropriate for this (acute) risk assessment.
This risk assessment is required.

1b. Acute Reference Dose (RfD) - General population including infants and children.

Study Selected: Developmental Study–Rat (§83-3a), MRID No.42942803
Dose and Endpoint for Establishing the RfD: The Maternal NOAEL is 10 mg/kg/day based on decreased maternal body weight seen during gestation day 6-8 after 3 dosages.
Uncertainty Factor (UF): 100

Acute RfD: $\frac{10 \text{ mg/kg}}{100 \text{ (UF)}} = \mathbf{0.1 \text{ mg/kg}}$

Comments about Study/Endpoint/Uncertainty Factor: The decreased maternal body weight was seen during gestation days 6-8 after 3 dosages. Therefore, this endpoint is considered to be appropriate for this (acute) risk assessment.
This risk assessment is required.

2. Chronic Dietary Reference Dose (RfD)

Study Selected: Chronic Toxicity/Carcinogenicity Study - Rat (§83-5),
MRID No.43593201.
Dose and Endpoint for establishing RfD: NOAEL = 10 mg/kg/day based on decreased body weight gains and liver hypertrophy at 30 mg/kg/day (LOAEL).
Comments about Study/Endpoint/Uncertainty Factor: The results of the 14-week feeding study in rats (MRID No. 42942802) with a NOAEL of 9.4 mg/kg/day and a LOAEL of 37 mg/kg/day and the Two-Generation Reproduction Study in rats (MRID 43190301) with a NOAEL of 10 mg/kg/day and a LOAEL of 30 mg/dg/day provide support for the critical study.
Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intra-species variability.

Chronic RfD: $\frac{10 \text{ mg/kg}}{100 \text{ (UF)}} = \mathbf{0.10 \text{ mg/kg}}$

3. Occupational/Residential Exposure

a. Dermal Absorption

Dermal Absorption Factor: 60 %

No dermal absorption studies are available. The estimated dermal absorption rate of 60% is based on results of an oral developmental toxicity study in rabbits and a 21-day dermal toxicity study in rabbits. A ratio of the LOAELs from the oral and dermal studies indicated an approximate absorption rate of 60% (oral LOAEL 600 mg/kg/day/dermal LOAEL of >1000 mg/kg/day x 100=60%).

b. Short-Term Dermal (1-7 days)

Study Selected: Oral Developmental Toxicity–Rat (§82-1a),
MRID No.42942803
Dose and Endpoint Proposed for Consideration: The developmental NOAEL is 10 mg/kg/day based on decreased fetal body weights at 40 mg/kg/day (LOAEL).
Comments about Study/Endpoint: Although a 21-day dermal toxicity study in rabbits with a NOAEL of 1000 mg/kg/day is available, the HIARC selected an oral (developmental) NOAEL because of the concern for the developmental effects seen in three species (mice, rat, and rabbits). Since an oral NOAEL was selected, a 60% dermal absorption factor should be used for risk assessment
This risk assessment is required.

c. Intermediate-Term Dermal (7 days to several months)

Study Selected: 14-Week Oral Toxicity Study - Rats (§82-1a),
MRID No.42942802
Dose and Endpoint for risk Assessment: The NOAEL is 9.4 mg/kg/day based on reduced body weight gains and histopathological changes in the bone marrow, liver, and thyroid at 37 or/40 mg/kg/day (LOAEL).
Comments about Study/Endpoint: A 21-day dermal toxicity study in rabbits is available. However, no effects were seen at the highest dose (1000 mg/kg/day). An oral value was selected because: 1) of the consistent pattern in the effect observed (i.e., decrease in body weight gain) in the chronic study at the same LOAEL (40 mg/kg/day); and, 2) the duration of this study is appropriate for this exposure period of concern (i.e., 7-days to several months). Since an oral NOAEL was selected , a dermal absorption factor of 60% should be used for this risk assessment.
This risk assessment is required.

d. Long-Term Dermal (Several months to life-time)

Study Selected: Chronic Toxicity/Carcinogenicity Study - Rat (§83-5a),

MRID No. 43593201.
Dose and Endpoint for Risk Assessment: NOAEL = 10mg/kg/day based on decreased body weight gains and liver hypertrophy at 30 mg/kg/day (LOAEL).
Comments about Study/Endpoint: Chronic dermal exposure to thiabendazole may be likely for some industrial preservative uses. If there is no potential for chronic dermal exposure to thiabendazole, then this risk assessment is not required. However if there is a potential for dermal exposure, then the above dose/endpoint should be used. This dose/endpoint/study was used to establish the chronic RfD. Since an oral value was selected, 60% dermal absorption should be used.
This risk assessment is required.

e. Inhalation Exposure

Thiabendazole is non volatile at room temperature. There is no potential for acute and intermediate-term duration exposure. However, chronic inhalation exposure to thiabendazole may be likely for some industrial preservative uses.

Study Selected: Chronic toxicity/Carcinogenicity Study - Rat (§83-5a), MRID No.43593201
Dose and Endpoint Proposed for Risk assessment: NOAEL = 10 mg/kg/day based on decreased body weight gains and liver hypertrophy at 30 mgm/kg/day (LOAEL)
Comments about Study/Endpoint: There are no inhalation toxicity studies available. The acute inhalation studies are waived. Therefore, HIARC selected the oral values for inhalation risk assessment.
Inhalation Risk Assessment: Since the NOAEL selected for inhalation risk assessment are from oral studies, route to route extrapolation should be as follows:

(i) The inhalation exposure component (i.e. ug a.i./day) using a 100% absorption rate (default value) and an application rate should be converted to an equivalent oral dose (mg/kg/day)

This risk assessment is required.

f. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

A Margin of Exposure of 100 is adequate to ensure protection from occupational and exposure to thiabendazole by dermal and inhalation routes. There are no residential uses. Residential risk assessment is not required.

Recommendation for Aggregate Exposure Risk Assessments

Since there are no residential uses, aggregate exposure risk asessments will be limited to food plus water. For acute and chronic aggregate risk, combine the high end (for acute) and average (for chronic) values for food and water and compare it to the respective PADs.

Cancer Assessment

On May 25, 1999, the CARC determined that based on the evidence presented, thiabendazole was carcinogenic in rats. In a carcinogenicity study in Sprague-Dawley Crl:CD BR rats/sex/dose, there was an increase in the incidence of thyroid follicular cell adenoma detected in the mid- (5/44, 11%) and high-dose (6/34; 18%) males (vs 0/76 in controls) and the high-dose (5/50; 10%) females (vs 1/50 and 2/50 in controls).

The committee classified Thiabendazole as "likely to be a carcinogen to humans," and recommended a MOE approach for the quantification of human cancer risk.

FQPA Consideration

1. Special Sensitivity to Infants and Children

The oral perinatal and prenatal data revealed no evidence of increased susceptibility of rat, rabbit, or mouse fetuses to *in utero* exposure to thiabendazole.

2. Recommendation for a Developmental Neurotoxicity Study

The HIARC did not recommend that developmental neurotoxicity study be required for thiabendazole.

3. FQPA Safety Factor Committee Recommendation

The FQPA Safety Factor committee met on August 30, 1999 to evaluate hazard and exposure data for thiabendazole and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to thiabendazole. The FQPA Safety Factor Committee has determined that the 10x FQPA safety factor be removed in assessing the risk posed by this chemical. The rationale for removing the safety factor included: The Committee concluded that the safety factor could be removed for thiabendazole because: 1) The toxicology database is complete for FQPA assessment; 2) The toxicity data provide no indication of increased susceptibility of young rats or rabbits to thiabendazole; 3) The HIARC determined that a developmental neurotoxicity study is not required; 4) The exposure assessments will not underestimate the potential dietary (food and drinking water) exposures for infants and children from the use of thiabendazole; and 5) There are

currently no residential (non-occupational) uses of thiabendazole.

Data gaps

The available genotoxicity studies although acceptable are inadequate to fulfill the guideline requirements. A data gap exists for two *in vitro* studies namely, *in vitro* mammalian gene mutation and *in vitro* chromosome aberration assay. It was concluded, however, that since there is confirming evidence that thiabendazole is aneugenic, no further genetic toxicology testing is required. Requirements for a 90-day inhalation and neurotoxicity studies were waived by HED in 1993 (HED Doc. No. 010140) and 1988 (HED Doc. No. 006934), respectively.

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